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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WILDER, CYNTHIA B	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 10/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/758,936	BURKETT, DOUGLAS D.	
	Examiner	Art Unit	
	Cynthia B. Wilder, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Specification

1. The disclosure is objected to because of the following informalities:

(a) The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or
REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)
(e) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) BRIEF SUMMARY OF THE INVENTION.
(g) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(h) DETAILED DESCRIPTION OF THE INVENTION.
(i) CLAIM OR CLAIMS (commencing on a separate sheet).
(j) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(k) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

(b) (a)The use of the trademark "OraTest" at page 5 of the specification has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

(c) The specification is objected to because at pages 6 and page 12, the specification recites "Example 1". Thus it is confusing as to which of the Examples is indeed considered Example 1. Appropriate correction is required.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for early prediction of eventual development of oral and oropharyngeal squamous cancers, it does not reasonably provide enablement for a prognostic method for the early prediction of eventual development of any invasive cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The specification does not enable any person skilled in the art to which it pertains, or with which

it is most nearly connected, to make or use the invention commensurated in scope with the claim. The first paragraph of section 112 requires the specification describe how to make or use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue (See *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir, 1988)). These factor include, but are not limited to:

I. Quantity of Experimentation Necessary:

4. The claimed invention is drawn to a prognostic method for early prediction of eventual development of invasive cancer, said method comprising: (a) applying to tissue a staining dye that is selectively retained by mitochondria of neoplastic and preneoplastic cells; (b) identifying clonal patches of said tissue by visually examining said tissue for stained tissue sites; (c) resecting tissue in the locus of said clonal patches; and (d) determining whether DNA extracted from said resected tissue exhibits allelic losses or mutation of tumor suppressor genes. At pages 2 and 3 of the specification, Applicant discloses prior art teaching of the use of polymorphic markers to determine allelic losses and mutations of tumor suppressor genes which have been shown to be involved in the early detecting of invasive cancer progression. At page 5, Applicant cites the prior art teaching of the Mashberg protocol which is used an *in vivo* screening method to identify malignant lesion of the oral cavity. Beginning at page 12, Applicant discloses in Example 1, the conventional practice of the Mashberg protocol on lesion of the oral cavity. Applicant discloses in the example wherein tissues of the oral cavity are stained with a staining dye, clonal patches identified by tissues which retain the staining dye and tissues in the locus of said clonal patches removed for genetic alteration analysis. At page 16 of the specification,

Example 2, Applicant discloses wherein laser capture microdissection is performed to isolate cells and extract DNA from biopsy tissue samples. Applicant discloses further discloses wherein microsatelllite analysis is performed at three loci to determine allelic loss.

The specification fails to describe or disclose wherein the method is performed on preneoplastic or neoplastic cells of tissue samples related to any invasive cancers, such as e.g., breast, cervix, prostate, skin or etc. The specification only discloses wherein neoplastic or prenoplastic cells of the oral cavity are examined. The specification additionally does not describe or disclose wherein any conceivable mutation of tumor suppressor genes or any allelic loss is associated with the prediction of eventual development of the numerous cancers encompassed by the claims, such as breast cancer, cervical cancer, prostate cancer, colon cancer, lung cancer, etc. The specification does not provide any information to enable one of ordinary skill in the art to perform the prognostic method as claimed. Therefore, as to the quantity of experimentation required, one of skill in the art would have to design an experimental procedure for early prediction of eventual development of invasive cancer that is commensurate with the entire scope of the claims.

II. Amount of Direction and Guidance:

The specification does not provide a prognostic method for early prediction of eventual development of invasive cancer that bears a reasonable correlation to the entire scope of the claims. The Examples and description of the invention beginning at page 12, lack information concerning how the prognostic method is performed to determine the early prediction of eventual development of any invasive cancer. More specifically, the specification does not provide any

information wherein any mutation of any tumor suppressor gene or any allelic loss in any neoplastic or preneoplastic cells results in the early prediction of any invasive cancer. The specification does not describe the numerous cancers encompassed by the claims or the numerous mutations associated therewith. Therefore, undue experimentation would be required to practice the instant invention as claimed.

III. Presence and Absence of Working Examples:

The specification of the claimed invention lacks proper working examples. Beginning at page 12 of the specification, Applicant discloses preparation of clinical test solutions for screening of the oral cavity for lesions associated with oral cancer. At page 16 of the specification, Applicant discloses wherein positive lesions are biopsied and subjected to microsatellite analysis techniques to determine allelic loss.

Nowhere in the Examples or specification as whole is there a disclosure wherein a screening is performed on samples indicative of other forms of invasive cancers, besides the oral cavity. There is no indication from the specification that the method is capable of functioning to predict the eventual development of any of the many cancers that may progress into invasive carcinoma. Likewise there is no indication from the specification that any conceivable mutation of tumor suppressor genes or allelic loss is associated with determining early predictions of eventual development into invasive cancer. Merely making reference to the method as being a prognostic means of determining early prediction of eventual development of invasive cancer does not enable the practitioner to reproduce the results as reported in the specification for the broad scope of the claimed invention. Thus undue experimentation is clearly evident and required.

IV. Nature of the invention:

The nature of the invention is a prognostic method for early prediction of eventual development of invasive cancer, said method comprising the steps of: (a) applying to tissue a staining dye that is selectively retained by mitochondria of neoplastic and preneoplastic cells; (b) identifying clonal patches of said tissue by visually examining said tissue for stained tissue sites; (c) resecting tissue in the locus of said clonal patches; and (d) determining whether DNA extracted from said resected tissue exhibits allelic losses or mutation of tumor suppressor genes. The full scope of the claimed invention is not reproducible due to lack of guidance presented in the specification and Examples. As noted, the specification does not properly disclose a prognostic method for early prediction of eventual development of invasive cancer that bears a reasonable correlation to the entire scope of the claims.

V. Level of predictability and Unpredictability in the art:

The specification has not enabled a prognostic method for early prediction of eventual development of any invasive cancer commensurate in scope with the claims. Given the numerous cancers known in the prior art and numerous mutations associated with tumor suppressor gene functions, it would be highly unpredictable that any conceivable mutation of a tumor suppressor gene is capable of determining in any neoplastic or preneoplastic cell from any tissue source e.g., tissue from a toe, an early prediction of eventual development into invasive carcinoma. Additionally, the results of any modification to the claimed invention is unpredictable since a reasonable expectation of success is limited by a lack of knowledge concerning other cancer types, other tissue source, and functionality of mutations of tumor suppressor genes. Therefore, without sufficient knowledge and guidance, performing the prognostic method for

early prediction of eventual development of invasive cancer is unpredictable and the experimentation left to those in the art is unnecessarily and improperly extensive and undue.

For all of the foregoing reasons, undue experimentation is necessary for one of skill in the art to obtain the claimed invention.

Claim Rejections - 35 USC § 112 second paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Note* The preceding rejection is based on the broad interpretation of the term "resecting". While the specification at page 16 discloses that laser capture microdissection is used to isolate cells and extract DNA after identifying clonal patches, the specification does not provide a limiting definition for the term "resecting". Thus, in the context of the claim language, the term "resecting tissue" is broadly being interpreted simply as a tissue biopsy.

(a) Claim 1 lacks proper antecedent basis in the final step (d) for "determining whether DNA extracted from said resected tissue exhibits allelic losses..." because the prior steps do not indicate or recite wherein DNA has been extracted from a tissue. It is suggested amending the claims such that the method steps agree.

(b) Claim 1 is indefinite for failing to recite a final process step that clearly relates back to the preample. The claims are drawn to "a method for early prediction of eventual development of invasive cancer" yet the final step (d) recites "determining whether DNA extracted from said resected tissues exhibits allelic losses or mutations of tumor suppressor genes". The claims do

not set forth how determining allelic losses or mutations of tumor suppressor genes result in a prognosis of the early prediction of eventual development of invasive cancer. Thus it is unclear as to whether the claim is intended to be directed to a method for determining allelic losses or mutations of tumor suppressor genes in a sample or to a method for the early prediction of eventual development of invasive cancer. Clarification is required as to Applicant's intent.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mashberg et al. (A Cancer Journal for Clinicians, Vol. 45, No. 6, pages 328-351, Nov-Dec 1995) in view of Rosin et al. (Clinical Cancer Research, Vol. 6, pages 3557-362, Feb 2000). Claim 1 is broadly drawn to a prognostic method for early prediction of eventual development of invasive cancer, said method comprising: (a) applying to tissue a staining dye that is selectively retained by mitochondria of neoplastic and preneoplastic cells; (b) identifying clonal patches of said tissue by visually examining said tissue for stained tissue sites; (c) resecting tissue in the locus of said clonal patches; and (d) determining whether DNA extracted from said resected tissue exhibits allelic losses or mutation of tumor suppressor genes.

Mashberg et al teach a prognostic method for early prediction of eventual development of invasive cancer, said method comprising: (a) applying to tissue a staining dye (toluidine blue) that is selectively retained by mitochondria of neoplastic and preneoplatic cells; (b) identifying

clonal patches of said tissue by visually examining said tissue for stained tissue sites (page 345, section entitle "Vital Staining", col. 1, beginning at the second full paragraph to page 347, column 1, lines 1-3); (c) resecting tissue in the locus of said patches for subsequent analysis (page 347, beginning at col. 1, first full paragraph to page 349, column 1, lines 1-28). Mashberg et al teach that the staining dye is useful because it clinically stains neoplastic and preneoplastic cells (malignant and premalignant cells), but not normal mucosa (page 345, lines 28-29 and serves as a guide to biopsy by localizing tumor cells within the area of erythroplasia (page, 346, 13th through 15th lines from bottom of column 2).

The method of Mashberg et al differs from the instant invention in that Mashberg et al do not expressly teach wherein DNA is extracted from the resected tissue and examined for allelic losses or mutation of tumor suppressor genes. However, Mashberg et al provides motivation for subsequent analysis in the teaching that "a negative biopsy should not be accepted as the final word if a tissue sample is considered suspicious for malignancy". Thus Mashberg et al suggest further analysis and/or biopsy be performed on the suspected sample.

Rosin et al teach method for the analysis of a biopsy tissue sample to identify genetic changes critical to the progression and non-progression of premalignant lesions into invasive cancer. Rosin et al teach wherein the method comprises obtaining paraffin-embedded biopsy tissue samples confirmed by histological diagnosis and at least two pathologists as hyperplasia or mild or moderate dysplasia; microdissecting tissue in the locus of areas identified as hyperplasia, dysplasia, or tumor; extracting DNA from the dissected tissue and determining by polymerase chain-based microsatellite analysis whether the dissected tissue exhibits allelic losses (Abstract and page 358, col. 1, beginning at the second full paragraph (section entitle "sample collection)

to column 2, sections entitled "Tissue Microdissection and DNA Extraction" and "LOH analysis"). Rosin et al teach that this method is a more sensitive technique for studying clonal changes in tumors and premalignant lesions. Rosin et al further teach that the advantage of this procedure is that is requires only small quantities of DNA yet yields valuable data on the loss of chromosomal regions that contain putative suppressor genes. Rosin et al states that hence, information critical to genetic events can be obtained even before the identification of the actual suppressor gene (page 357, column 2, third full paragraph).

Therefore in view of foregoing, one of ordinary skill in the art at the time of the claimed invention would have been motivated to have combined the polymerase chain-based microsatellite analysis method of Rosin et al with the staining diagnosis method of Mashberg et al. as a prognostic method for the early prediction of eventual development of invasive cancer. One of ordinary skill in the art would have been motivated to do so for the advantages taught by Rosin et al that the polymerase chain-based microsatellite analysis method is a more sensitive technique for studying clonal changes in tumors and premalignant lesions in that the method requires only small quantities of DNA yet yields valuable data on the loss of chromosomal regions that contain putative suppressor genes (page 357, column 2, third full paragraph).

Conclusion

9. Claim 1 is not allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-0791. The examiner works a flexible schedule and can be reached by phone and voice mail.

Alternatively, a request for a return telephone call may be emailed to cynthia.wilder@uspto.gov. Since email communications may not be secure, it is suggested that information in such request be limited to name, phone number, and the best time to return the call.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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CYNTHIA WILDER
PATENT EXAMINER

10/12/2005